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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/700,712	11/13/2001	Nils Carlin	REF/CARLIN/509	7758

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Alexandria, VA 22314-1176

EXAMINER
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DEVI, SARVAMANGALA J N

ART UNIT	PAPER NUMBER
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1645

DATE MAILED: 07/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/700,712

Applicant(s)

CARLIN ET AL.

Examiner

S. Devi, Ph.D.

Art Unit

1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 14 April 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 17-23 ~~is~~ are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 17-23 ~~is~~ are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

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## **RESPONSE TO APPLICANTS' AMENDMENT**

### **Applicants' Amendments**

1) Acknowledgment is made of Applicants' amendments filed 04/14/05 and 01/24/05 in response to the non-final Office Action mailed 09/23/04. With this, Applicants have amended the specification.

### **Status of Claims**

2) Claims 1-16 have been canceled via the amendment filed 01/24/05.  
New claims 17-23 have been added via the amendment filed 01/24/05.  
Claims 17, 19 and 20 have been amended via the amendment filed 04/14/05.  
Claims 17-23 are pending and are under examination.

### **Objection(s) Withdrawn**

3) The objection to the specification made in paragraph 7(a) of the Office Action mailed 09/23/04 is withdrawn in light of Applicants' amendment to the specification.

### **Objection(s) Maintained**

4) The objection to the specification made in paragraph 7(b) of the Office Action mailed 09/23/04 is maintained for reasons set forth therein.

### **Rejection(s) Moot**

5) The rejection of claim 2 and those dependent therefrom made in paragraph 9 of the Office Action mailed 09/23/04 under 35 U.S.C § 101 as being directed to a non-statutory subject matter, is moot in light of Applicants' cancellation of the claim.

6) The rejection of claim 9 and those dependent therefrom made in paragraph 10 of the Office Action mailed 09/23/04 under 35 U.S.C § 101 as being directed to a non-statutory subject matter, is moot in light of Applicants' cancellation of the claim.

7) The rejection of claim 12 and those dependent therefrom made in paragraph 11 of the Office Action mailed 09/23/04 under 35 U.S.C § 101 as being directed to a non-statutory subject matter, is moot in light of Applicants' cancellation of the claim.

8) The rejection of claims 1-9, 12, 13 and 16 made in paragraph 13 of the Office Action

mailed 09/23/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claims.

9) The rejection of claims 9 and 12 made in paragraph 15 of the Office Action mailed 09/23/04 under 35 U.S.C. § 102(b) as being anticipated by Valle *et al.* (*Vibrio cholerae thyA* gene. XP-002118053. EMBL Accession no. Y17135, 01 May 1998 – Applicants' IDS), moot in light of Applicants' cancellation of the claims.

10) The rejection of claims 2 and 16 made in paragraph 16 of the Office Action mailed 09/23/04 under 35 U.S.C. § 102(b) as being anticipated by Attridge *et al.* (*Microbial Pathogenesis* 19: 11-18, 1995 - Applicants' IDS), is moot in light of Applicants' cancellation of the claims.

11) The rejection of claims 2 and 16 made in paragraph 17 of the Office Action mailed 09/23/04 under 35 U.S.C. § 102(b) as being anticipated by Mahan *et al.* (US 5,434,065), is moot in light of Applicants' cancellation of the claims.

12) The rejection of claims 2-7 made in paragraph 18 of the Office Action mailed 09/23/04 under 35 U.S.C. § 102(b) as being anticipated by Morona *et al.* (EP 0,251,579 – Applicants' IDS), is moot in light of Applicants' cancellation of the claims.

13) The rejection of claim 8 made in paragraph 20 of the Office Action mailed 09/23/04 under 35 U.S.C. § 103(a) as being unpatentable over Morona *et al.* (EP 0,251,579) in view of Arntzen *et al.* (US 6,194,560), is moot in light of Applicants' cancellation of the claim.

14) The rejection of claims 1 and 16 made in paragraph 21 of the Office Action mailed 09/23/04 under 35 U.S.C. § 103(a) as being unpatentable over Valle *et al.* (*Vibrio cholerae thyA* gene. XP-002118053. EMBL Accession no. Y17135, 01 May 1998 – Applicants' IDS) in view of Morona *et al.* (EP 0,251,579 – Applicants' IDS), is moot in light of Applicants' cancellation of the claims.

15) The rejection of claim 13 made in paragraph 22 of the Office Action mailed 09/23/04 under 35 U.S.C. § 103(a) as being unpatentable over Valle *et al.* (*Vibrio cholerae thyA* gene. XP-002118053. EMBL Accession no. Y17135, 01 May 1998 – Applicants' IDS) in view of Morona *et al.* (EP 0,251,579 – Applicants' IDS) in view of Prakash *et al.* (US 6,251,866), is moot in light

of Applicants' cancellation of the claim.

### **Response to Applicants' Arguments With Regard to Morona's Reference**

**16)** With regard to the teachings of Morona *et al.*, Applicants contend that Morona *et al.* disclose selection of mutant strains, i.e., point mutations in the strain, but not defined *thyA* mutants of *Vibrio cholerae* as in the present case. Applicants point to lines 6-16 on page 2 of the specification and state that the strains of Morona *et al.* 'may' revert to wild-type at unacceptable high frequencies. Applicants state that the Office Action is not correct in stating that the mutant strain grows on a media containing no thymine. Applicants further submit that all claims have been cancelled without prejudice or disclaimer and therefore the rejections have been obviated.

Applicants' arguments have been carefully considered, but are not persuasive. It should be noted that a spontaneous *thyA*- mutant of *Vibrio cholerae* expressing a homologous or heterologous protein is not excluded from the scope of the claims. The instantly claimed *thyA* mutants of *Vibrio cholerae* are not recited to be non-revertible carrying a defined mutation. In fact, Morona *et al.* taught that the cloned DNA fragment inserted in their strain is a non-reverting *thyA*<sup>+</sup> gene (see part (b) at the end of page 2). Furthermore, the *thyA* mutation is recognized in the art as a non-reverting mutation. See part (b) under 'RESULTS' on page 134 of Attridge *et al.* (In: *Proceed. Aust. Biotechnol. Conf. 8 Meeting.* pages 134-139, 1989). The new claims are still anticipated by Morona *et al.* See art rejections below.

### **Rejection(s) under 35 U.S.C. § 112, Second Paragraph**

**17)** Claims 17-23 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 17 is vague, indefinite, confusing and has incorrect antecedence in the recitation: 'the one or several episomal autonomously replicating DNA elements further comprising' (see lines 5 and 6). The earlier part of the claim includes the recitation: 'at least one episomal autonomously replicating DNA element' (see line 3). For proper antecedence, it is suggested that Applicants replace the phrase with: --wherein the at least one episomal autonomously replicating DNA element further comprises--.

(b) Claim 18 is confusing and/or incorrect in the phrase: 'has been deprived of its *thy*

*A* gene by site-directed mutagenesis in the *V. Cholerae* chromosome **for the** deletion and/or insertion of nucleotides at the locus of the *thy A* gene' [Emphasis added]. It is unclear what is being conveyed in this phrase. Does a partial deletion and/or insertion of nucleotides at the locus of the *thy A* gene result in a strain of *Vibrio cholerae* that is 'deprived of its *thy A* gene'?

(c) Claim 21 is indefinite and confusing in the limitation: 'the foreign *thy A* gene is an *E. coli* gene'. The scope of '*thy A* gene' is not the same as that of the generically recited 'gene'. For the purpose of distinctly claiming the subject matter of the invention, it is suggested that Applicants replace the limitation with: --the foreign *thy A* gene is *E. coli thy A* gene--.

(d) Claim 23 is indefinite and confusing in the limitation: 'some natural or unnatural nucleotide extensions, truncations, deletions or additions', because it is unclear what quantity is encompassed in the limitation 'some', and what changes are encompassed in the limitation: 'natural or unnatural nucleotide extensions'.

(e) Claim 23 is vague, indefinite and confusing in the limitation: 'the *thy A* gene of the chromosome has the nucleotide sequence SEQ ID NO: 1, or said nucleotide sequence ..... that do not interfere with the natural function of the nucleotide sequence'. Claim 23 depends from claim 17, which is drawn to a *Vibrio cholerae* strain that is 'deprived of its *thy A* gene in the chromosome and thus lacking the functionality of the *thy A* gene'. The dependent claim 23 however recites that the *Vibrio cholerae* strain of claim 17 **has** the *thy A* gene of the chromosome having the nucleotide sequence SEQ ID NO: 1 or the SEQ ID NO: 1 having some extensions, truncations, deletions or additions that do not interfere with the 'natural function of the nucleotide sequence'. A nucleotide sequence whose natural function is not interfered would be naturally functional. It is unclear how a *Vibrio cholerae* strain that is recited to be 'deprived of its *thy A* gene in the chromosome and thus lacking the functionality of the *thy A* gene' in the base claim can have a chromosomal gene, or a nucleotide sequence carrying changes 'that do not interfere with the natural function of the nucleotide sequence'.

(f) Claims 19-23, which depend directly or indirectly from claim 17, are also rejected as being indefinite because of the indefiniteness identified above in the base claim.

### **Rejection(s) under 35 U.S.C. § 102**

**18)** Claims 17-21 and 23 are rejected under 35 U.S.C. § 102(b) as being anticipated by

Morona *et al.* (EP 0,251,579 – Applicants' IDS).

Morona *et al.* disclosed a mutant strain of *Vibrio cholerae* defective (i.e., lacking functionality) in the *thyA*<sup>+</sup> gene. The mutant *thyA*<sup>-</sup> *Vibrio cholerae* strain, utilizable in a live oral vaccine, is transformed with a plasmid (i.e., an episomal autonomously replicating DNA element) into which is cloned an *E. coli thyA* gene (i.e., foreign *thyA*), and therefore has a functional *thyA* gene that enables the strain to grow in the absence of thymine in the growth medium. The *thyA* inactivation is by insertion of the DNA fragment containing a non-reverting *thyA*<sup>+</sup> gene. The plasmid used for transformation of the mutant bacterial strain further comprises a gene element that expresses an antigen, such as, an outer membrane protein antigen or the O-antigen determinant of a disease of interest (see claims 18 and 17; part (b) at the end of page 2; and columns 5 and 6, including first and second full paragraphs in column 6). Morona's mutant strain of *Vibrio cholerae* defective (i.e., lacking functionality) in the *thyA*<sup>+</sup> gene is viewed as inherently carrying nucleotides deleted or inserted at the locus of the *thyA* gene by naturally occurring site-directed mutagenesis. That the *thyA* gene of the prior art *Vibrio cholerae* has the nucleotide sequence of SEQ ID NO: 1 or a variant thereof having 'some' natural or unnatural nucleotide extensions, truncations, deletions or additions that do not interfere with the natural function of the nucleotide sequence, is inherent from the teachings of Morona *et al.* since the *thyA*<sup>+</sup> gene is well known in the art to be very conserved, being found in prokaryotes, eukaryotes, bacteriophages and other bacteria such as *E. coli* and *Salmonella* (see third full paragraph in column 2 and first full paragraph in column 6 of Morona *et al.*).

Claims 17-21 and 23 are anticipated by Morona *et al.*

### **Rejection(s) under 35 U.S.C. § 103**

**19)** Claim 22 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Morona *et al.* (EP 0,251,579 – Applicants' IDS) in view of Arntzen *et al.* (US 6,194,560, already of record).

The reference of Arntzen *et al.* is applied in this rejection because it qualifies as prior art under subsection (e) of 35 U.S.C. § 102 and accordingly is not disqualified under U.S.C. 103(a).

The teachings of Morona *et al.* have been explained above which do not disclose that their mutant *Vibrio cholerae* encodes *E. coli* LTB.

However, fusion of the *E. coli* LTB to a nucleotide sequence encoding an antigen in a

recombinant bacterial strain and co-expression of the antigen along with LTB was well known in the art at the time of the invention. For instance, Arntzen *et al.* taught the routine and conventional fusion of *E. coli* LTB to sequences that encode other antigens for co-expression of both, since LTB has the advantageous property of serving both as an antigen and as an adjuvant (see first full paragraph in column 14; and lines 37-41 in column 15).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention as made to fuse Arntzen's *E. coli* LTB gene into the antigen expressing gene element of Morona's mutant *Vibrio cholerae* strain to produce the instant invention with a reasonable expectation of success. One of skill in the art would have been motivated to produce the instant invention for the expected benefit of advantageously enhancing immune response of the antigen(s) expressed by Morona's mutant *Vibrio cholerae* strain by co-expression with *E. coli* LTB, which LTB is known in the art to serve as an adjuvant in addition to serving as an antigen as taught by Arntzen *et al.*

Claim 22 is *prima facie* obvious over the prior art of record.

### Objection(s)

20) Claims 18 and 23 are objected to for the following reasons:

(a) Claim 18 is objected to for the incorrect limitation '*V. Cholerae*' (see line 2), which limitation is inconsistent with the correct art-accepted recitation used in claims 17, 21 and 22: --*V. cholerae*--.

(b) Claim 23 is indefinite and confusing in the limitation: 'the *thy A* gene of the chromosome has the nucleotide sequence SEQ ID NO: 1'. For clarity, it is suggested that Applicants replace the phrase with: --the *thy A* gene in the chromosome has the nucleotide sequence of SEQ ID NO: 1--.

### Remarks

21) Claims 17-23 stand rejected.

22) Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE



MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

**23)** Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The Fax number for submission of amendments, responses or papers is (703) 872-9306.

**24)** Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.Mov>. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

**25)** Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

June, 2005